

NEUROTROPHIC FACTORS AND THEIR RECEPTORS IN CENTRAL CATECHOLAMINE SYSTEMS:
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Both the nerve growth factor (NGF)-related and epidermal growth factor (EGF)-related families of polypeptide growth factors have been shown to support the survival, differentiation and maintenance of several neuronal populations within the central nervous system (CNS). In particular, members of both families are neurotrophic and neuroprotective for certain catecholamine neurons, including those of the dopaminergic ventral mesencephalon and the noradrenergic locus coeruleus. Work in this laboratory has been directed at determining the organization and regulation of these trophic factors and their receptors within catecholamine systems *in vivo*. Double-labeling studies indicate that adult rat midbrain dopaminergic neurons synthesize mRNAs for the neurotrophins brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), as well as for their tyrosine kinase receptors *trkB* and *trkC*, respectively. These results support the notion that BDNF and NT-3 influence dopaminergic neurons via autocrine or paracrine mechanisms. Acute lesion of the nigrostriatal pathway with the catecholamine-specific neurotoxin 6-hydroxydopamine (6-OHDA) resulted in the transient increased expression of BDNF mRNA, and decreased expression of NT-3 mRNA, within neurons of the substantia nigra and ventral tegmental area. The early transient response of BDNF to toxic insult may reflect a potential neuroprotective role for the neurotrophin *in vivo*. Both *trkB* and *trkC* mRNAs are broadly distributed throughout the striatum. Long-term lesion of the nigrostriatal pathway resulted in the increased expression of *trkB*, but not *trkC*, mRNA in the caudate-putamen, indicating that midbrain dopaminergic afferents selectively regulate *trkB* mRNA levels in the striatum. The EGF receptor (EGF-R) ligand transforming growth factor- α (TGF α) is also expressed within the striatum, suggesting a typical target-derived trophic role for midbrain dopamine neurons, which express EGF-R mRNA. Lesion of the nigrostriatal pathway led to the decreased expression of TGF α mRNA in the caudate-putamen. Taken together, these data suggest that dopaminergic afferents normally inhibit the expression of *trkB*, and enhance the expression of TGF α , in the target striatum. Intriguing recent data indicate that a single injection of BDNF into the dopamine-depleted striatum, followed by a one-week survival period, normalizes the altered expression of both *trkB* and TGF α mRNAs within the striatum. The neurotrophins BDNF and NT-3 and their receptors are also expressed by noradrenergic locus coeruleus neurons. Studies to date indicate that the catecholamine-depleting agent reserpine, as well as traumatic injury to the brain or spinal cord, induce a substantial regulation of BDNF mRNA, and downregulation of NT-3 mRNA, within neurons of the locus coeruleus. Overall, the above data raise the possibility of select trophic factor involvement in neurological disorders associated with central catecholamine systems, including Parkinson's disease, schizophrenia, anxiety and depression. This work was supported in part by grants from the National Parkinson Foundation, American Parkinson Disease Association, Scottish Rite Schizophrenia Research Program, and NS35164.